

Original article

Epidemiology and classification of gastroenteropancreatic neuroendocrine neoplasms using current coding criteria

O. M. Sandvik^{1,5}, K. Søreide^{1,5}, E. Gudlaugsson², J. T. Kvaløy^{3,4} and J. A. Søreide^{1,5}

Departments of ¹Gastrointestinal Surgery, ²Pathology and ³Research, Stavanger University Hospital, and ⁴Department of Mathematics and Natural Sciences, University of Stavanger, Stavanger, and ⁵Department of Clinical Medicine, University of Bergen, Bergen, Norway

Correspondence to: Professor J. A. Søreide, Department of Gastrointestinal Surgery, Stavanger University Hospital, PO Box 8100, N-4068 Stavanger, Norway (e-mail: jonarne.soreide@uib.no)

Background: The lack of uniform criteria for coding of gastroenteropancreatic neuroendocrine neoplasia (GEP-NEN) has hampered previous epidemiological studies. The epidemiology of GEP-NEN was investigated in this study using currently available criteria.

Methods: All patients diagnosed with GEP-NEN between January 2003 and December 2013 in a well defined Norwegian population of approximately 350 000 people were included. Age- and sex-adjusted incidence rates were calculated. The current 2010 World Health Organization criteria, European Neuroendocrine Tumour Society classification and International Union Against Cancer (UICC) classification were used.

Results: A total of 204 patients (114 male, 55.9 per cent) were identified. The median age at diagnosis was 61 (range 10–94) years. The annual overall crude incidence was 5.83 per 100 000 inhabitants, with an increasing trend ($P = 0.033$). The most frequent location was small intestine (60 patients, 29.4 per cent) followed by appendix (48 patients, 23.5 per cent) and pancreas (33 patients, 16.2 per cent). Grade 1 tumours were more common in gastrointestinal (100 patients, 58.5 per cent) than in pancreatic (9 patients, 27 per cent) NEN. According to the UICC classification, 77 patients (37.7 per cent) had stage I, 17 patients (8.3 per cent) stage II, 37 patients (18.1 per cent) stage III and 70 patients (34.3 per cent) had stage IV disease. No patient with stage I disease had grade 3 tumours; advanced tumour grade increased with stage.

Conclusion: A high crude incidence of GEP-NEN, at 5.83 per 100 000 inhabitants, was noted together with a significant increasing trend over time.

Presented in part to the 12th European Neuroendocrine Tumour Society Congress, Barcelona, Spain, March 2015; published in abstract form as *Neuroendocrinology* 2015; **102**: 92

Paper accepted 17 September 2015

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.10034

Introduction

Gastroenteropancreatic neuroendocrine neoplasia (GEP-NEN) originates from the diffuse neuroendocrine cell system of the gastrointestinal tract and pancreas, and represents 1–1.5 per cent of all GEP neoplasms^{1,2}. This heterogeneous group of epithelial neoplasms is highly variable in its clinical presentation, malignant potential and prognosis³.

In 1867, the neuroendocrine tumour (NET) was first described as a specific entity⁴. A system for tumour classification was initially developed⁵, but the nomenclature for this entity has been inconsistent. Numerous classification systems for staging and grading based on embryology,

morphology or biochemistry have been proposed, with none gaining robust acceptance over time^{5–7}.

The current 2010 World Health Organization (WHO) classification of GEP-NEN is based on histological grade and derived from degree of differentiation and the Ki-67 index, as proposed by the European Neuroendocrine Tumour Society (ENETS) in 2006 and 2007^{8–10}. Other characteristics, including tumour size and location and presence of metastases, are incorporated into the ENETS 2006–2007 TNM system^{8,9}. In 2009, the International Union Against Cancer (UICC) published another TNM system for tumour staging¹¹. By the introduction of a uniform nomenclature and classification system for

GEP-NEN, improved and comparable epidemiological data should eventually be available. In the past the epidemiology of GEP-NEN has been examined based on regional and national registries in Europe, the USA and Asia^{12–26}.

To circumvent many of the shortcomings of previous studies regarding definitions and reporting, this cohort study evaluated the epidemiological characteristics of patients diagnosed with GEP-NEN based on the most recent WHO and ENETS/UICC classifications, using a population-based, single-institution, consecutive series of patients treated over a decade.

Methods

This manuscript was completed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement²⁷. The Hospital Review Board approved the study (2011/1659-16) according to the general guidelines provided by the Regional Ethics Committee.

Population sample

Stavanger University Hospital, as the only hospital in the region, serves a catchment area of 18 municipalities in south-western Norway. It provides healthcare services to a well defined population that has increased from approximately 290 000 inhabitants in 2003 to more than 350 000 in 2014²⁸. The study included all patients initially diagnosed with GEP-NEN in this region during the 11-year interval from 1 January 2003 to 31 December 2013. All permanent residents of Norway are assigned an 11-digit identification number in the National Population Registry. Any change of address must be reported to the National Population Registry within 8 days of moving. The hospital's patient administrative system is linked electronically to the National Population Registry²⁸, enabling continued contact for follow-up assessments.

Identification of patients

Eligible patients were identified through a review of all NEN diagnoses recorded in the hospital's electronic pathology files. The data files were searched for histopathological or cytological diagnoses according to the Systematized Nomenclature of Medicine (SNOMED) classification system (Norwegian version) (topography T56/59/62-68; diagnosis M80411-3+6/M82401-6/M82431-3/M82441-3/M82451/M82461-3+6). Neuroendocrine neoplasms of the gastrointestinal tract and pancreas were identified. Lesions with histomorphology

and immunohistochemistry (IHC) profiles consistent with GEP-NEN were included. Where necessary, histology was re-evaluated, particularly with regard to the completeness of the IHC data (chromogranin A, synaptophysin, Ki-67, thyroid transcription factor 1 and CDX2, among others) and the proportion of different histological components in mixed adenoneuroendocrine carcinoma (MANEC).

Neuroendocrine liver tumours (labelled unknown) were included when an extrahepatic tumour outside the abdomen could be excluded via imaging or when the IHC profile did not suggest a primary lung tumour. All patients who underwent somatostatin receptor scintigraphy at the hospital during the study were reviewed to identify eligible patients with NEN not confirmed by histology. A search for eligible patients from the Stavanger University Hospital catchment area was also undertaken at a collaborating institution (Haukeland University Hospital, Bergen).

Patients diagnosed with primary non-gastrointestinal NEN, including lung, Merkel cell carcinomas, prostate, urinary bladder, uterus, breast, head and neck or otherwise misclassified tumours (by either location or histopathology), were excluded from the analysis.

Patient demographics and clinical information, including date of diagnosis, location of tumours and presence of regional and/or distant metastases, were retrieved from hospital records, autopsy reports, and information from general practitioners and the National Population Registry²⁸. The tumour characteristics recorded were: size, mitotic count (per high-power field) and the expression of Ki-67 (in 'hot spots'), synaptophysin and chromogranin A by IHC.

Definitions

The patients were grouped according to the 2010 WHO classification²⁹ (Table 1), and staged according to the 2006–2007 ENETS^{8,9} and 2009 UICC¹¹ criteria for TNM classification, for comprehensive and comparable reporting. In MANEC, both the high-grade neuroendocrine and the adenocarcinoma proportion exceed 30 per cent.

Annual age- and sex-adjusted incidence rates were calculated by direct standardization with 5-year intervals for age (with an open-ended interval from 85 years or more) using the World³⁰, USA 2000³¹, WHO³² and European 2013³³ standard populations, along with the Norwegian population (for each year) retrieved from Statistics Norway²⁸, as references. The population size for each year was the calculated average of the population at the beginning and end of the year.

Table 1 2010 World Health Organization classification of gastroenteropancreatic neoplasia

	Mitoses (per 10 HPFs)	Ki-67 index
Neuroendocrine tumour		
Grade 1 (carcinoid)	< 2	≤ 2
Grade 2	2–20	3–20
Neuroendocrine carcinoma		
Grade 3 – large cell or small cell type	> 20	> 20
Mixed adenoneuroendocrine carcinoma		
Hyperplastic and preneoplastic lesions		

At least 50 high-power fields (HPFs) counted (2 mm², original magnification ×40). Ki-67 immunoreactivity evaluated in 'hot spots'.

Statistical analysis

SPSS® version 22.0.0.0 for Mac (IBM, Armonk, New York, USA) and R3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis. Non-parametric tests were used for comparisons between subgroups, and log-linear Poisson regression analysis to test for differences in crude incidence over the study interval. To calculate age- and sex-adjusted incidence, the epitools package in R 3.1.0 was used³⁴. All tests were two-sided, and $P < 0.050$ was considered significant.

Results

A total of 204 patients with GEP-NEN were identified, including 198 (97.1 per cent) with a confirmed histopathological diagnosis. Six patients (2.9 per cent) were included based on convincing clinical findings: a raised level of serum chromogranin A and positive imaging findings (CT and somatostatin receptor scintigraphy). The search at Haukeland University Hospital identified three patients.

A male predominance was observed (114 patients, 55.9 per cent; $P = 0.017$). Patient demographics are summarized

in Table 2. Age at diagnosis did not differ between men and women (median age 61.5 and 60.5 years respectively; $P = 0.344$).

Patients with NEN of the appendix were significantly younger than those with tumours at other sites (median age 30 years for appendix *versus* 64 years for other locations; $P < 0.001$). In addition, patients with WHO grade (G) 1 NETs were significantly younger than those with G2 NETs and G3 neuroendocrine carcinomas (NECs) (median age 55.1 *versus* 65.3 and 66.2 years respectively; $P < 0.001$).

Incidence by sex and time

The annual overall crude incidence was 5.83 per 100 000 inhabitants (6.47 and 5.19 per 100 000 for men and women respectively). Standardized directly to the Norwegian population, the annual incidence rate was 6.62 per 100 000 inhabitants, with rates of 7.41 and 5.83 per 100 000 for men and women respectively.

The annual adjusted incidence rates standardized for different populations are shown in Table 3. Regardless of the standard population employed, the incidence remained high, and varied between a low annual crude incidence of 2.37 per 100 000 in 2004 to the highest incidence of 8.35 per 100 000 in 2009 (Fig. 1), with an increasing trend during the study period ($P = 0.033$).

Men were more frequently diagnosed with small intestinal ($P < 0.001$) and duodenal ($P = 0.011$) NEN, whereas tumours of unknown origin were more frequently found in women ($P = 0.004$) (Table 2).

Incidence by location

Almost one-third of the primary tumours (60, 29.4 per cent) were located in the small intestine (excluding the duodenum but including 2 NETs in Meckel's diverticulum), and the appendix was the second most common tumour

Table 2 Clinical characteristics according to tumour location

	Overall	Sex		All	Median (years)*		Crude incidence (per 100 000)		
		Male	Female		Male	Female	All	Male	Female
All	204 (100)	114 (55.9)	90 (44.1)	61 (10–94)	61.5 (13–94)	60.5 (10–88)	5.83	6.47	5.19
Oesophagus	3 (1.5)	1 (33)	2 (67)	76 (69–83)	76	76	0.09	0.06	0.12
Stomach	11 (5.4)	8 (73)	3 (27)	66 (35–94)	64	69	0.31	0.45	0.17
Duodenum	5 (2.5)	5 (100)	0 (0)	68 (47–76)	68	–	0.14	0.28	–
Small intestine	60 (29.4)	40 (67)	20 (33)	64 (48–91)	63	72	1.72	2.27	1.15
Appendix	48 (23.5)	22 (46)	26 (54)	30 (10–85)	33	29	1.37	1.25	1.50
Colon	15 (7.4)	9 (60)	6 (40)	62 (42–84)	59	71	0.46	0.51	0.35
Rectum	18 (8.8)	8 (44)	10 (56)	58 (37–84)	48	61	0.51	0.45	0.58
Pancreas	33 (16.2)	20 (61)	13 (39)	61 (20–85)	60	61	0.94	1.13	0.75
Bile duct	2 (1.0)	0 (0)	2 (100)	51 (23–80)	–	51	0.06	–	0.12
Unknown	9 (4.4)	1 (11)	8 (89)	78 (48–87)	63	80	0.26	0.06	0.46

Values in parentheses are percentages unless indicated otherwise; *values are median (range).

Table 3 Incidence rates of gastroenteropancreatic neoplasia, with adjusted rates related to common reference populations

	Incidence (per 100 000 per year)					
	Crude	Norway	World	WHO	USA 2000	Europe 2013
All	5.83	6.62	4.43	4.86	5.68	7.64
Male	6.47	7.41	4.83	5.40	6.15	9.08
Female	5.19	5.83	4.02	4.31	5.23	6.20

WHO, World Health Organization.

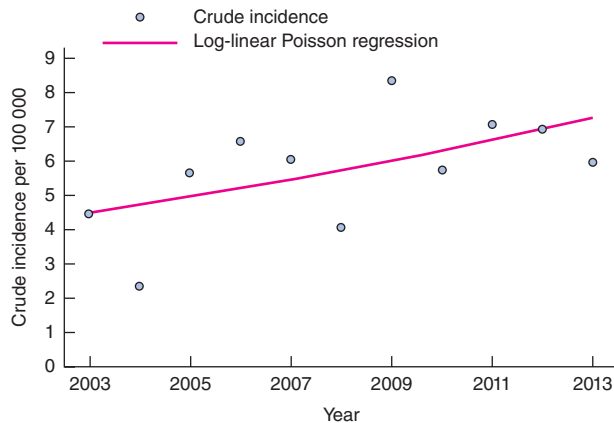


Fig. 1 Annual incidence per 100 000 by year in the study period. Poisson regression analysis shows a statistically significant increase in the annual crude incidence ($P = 0.033$)

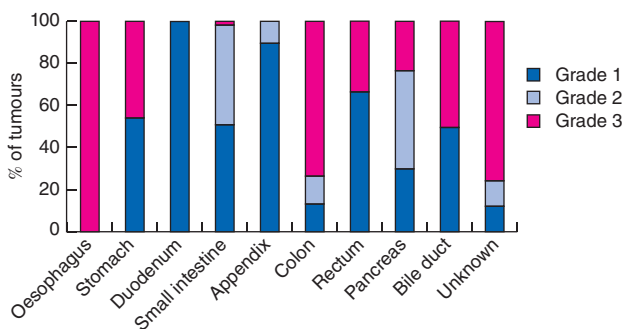


Fig. 2 World Health Organization tumour grade by organ. Of note is the wide variation in tumour grade between locations; low-grade tumours are most commonly encountered in the duodenum, small intestine and appendix

site (48, 23.5 per cent) (Table 2). A sixth of the tumours (33, 16.2 per cent) originated in the pancreas, including three tumours in patients with multiple endocrine neoplasia type 1 syndrome (MEN-1).

Multiplicity, defined as primary NEN in two different organs, was found in three patients: in the duodenum and stomach in one patient, the small intestine and appendix in another, and the pancreas and duodenum in a third patient

with MEN-1. Multifocal tumours in the small intestine were encountered in 21 (35 per cent) of 60 patients.

Tumour grade and stage at diagnosis

A total of 109 patients (53.4 per cent) had G1 NETs, 49 (24.0 per cent) had G2 NETs, and 40 (19.6 per cent) patients were diagnosed with G3 NEC. Male and female patients were distributed similarly across grades. The annual incidence rates for G1 tumours were 3.51 and 2.71 per 100 000 males and females respectively. For G2 tumours, respective rates for males and females were 1.53 and 1.27 per 100 000, and for G3 they were 1.30 and 0.98 per 100 000. Grade distribution for different locations is shown in Fig. 2. Grade 1 tumours were more common in gastrointestinal (100 patients, 58.5 per cent) than in pancreatic (nine patients, 27 per cent) NEN. All duodenal and appendiceal tumours, and most small intestinal (57 of 60), pancreatic (23 of 33) and rectal (12 of 18) tumours, showed G1/G2 differentiation. All three oesophageal NETs, a majority of the colonic NETs (11 of 15) and six of nine NETs with an unknown primary tumour site showed G3 differentiation. Four of the G3 NECs were classified as MANECs. Two appendiceal tumours were diagnosed as goblet cell carcinoids, which are currently regarded as a specific entity^{35,36}. This entity should no longer be classified as a NEN (ENETS, personal communication, 2015).

Half of patients (98, 48.0 per cent) had regional lymph node metastases, and more than one-third (70, 34.3 per cent) had distant organ metastases (liver, lung and distant lymph nodes) at the time of diagnosis. Ten of 15 patients with colonic NEN presented with distant organ metastases, whereas only one of the 48 patients with a primary appendiceal NEN had distant metastases. Regional lymph node involvement was present in most patients with NEN in the small intestine (52 of 60) and colon (12 of 15).

According to the UICC classification, 77 patients (37.7 per cent) had stage I, 17 patients (8.3 per cent) stage II, 37 patients (18.1 per cent) stage III and 70 patients (34.3 per cent) had stage IV disease. No patient with stage I disease had grade 3 tumours; advanced tumour grade increased with stage. The distribution of tumour

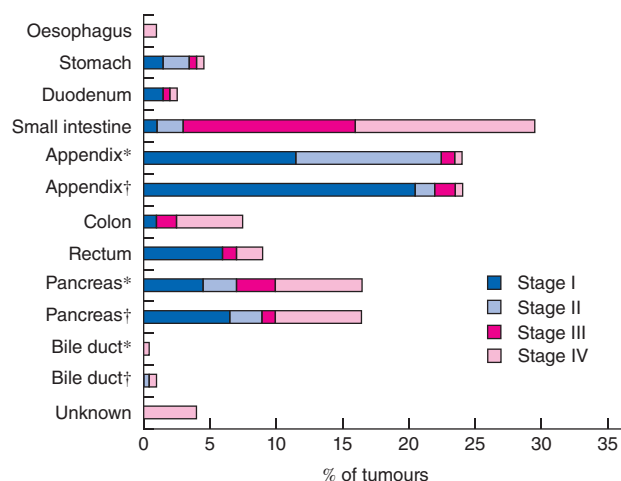


Fig. 3 Distribution by tumour location according to stage at the time of diagnosis. *European Neuroendocrine Tumour Society (ENETS) criteria (based on 200 patients; lack of information for staging in 4 patients). †International Union Against Cancer (UICC) criteria (based on 201 patients; lack of information for staging in 3 patients). Where the ENETS and UICC criteria are similar for a given location, a single column is presented. Otherwise, data for the two classification systems are shown separately

location by stage according to the UICC classification and ENETS criteria is presented in Fig. 3. There was notable discordance with respect to these staging systems for appendiceal and pancreatic neoplasms.

Discussion

The incidence of GEP-NEN obtained from south-western Norway is among the highest reported in the literature²² and increased significantly over the study interval. The present population-based study contributes to understanding of the true epidemiology of GEP-NEN. The increasing trend is in line with other studies from the USA and Europe^{17,37,38}. The high incidence reported in this study may seem an outlier. However, a previous Swedish autopsy study²⁶ reported an annual incidence of 8.4 NETs per 100 000 inhabitants (including fewer than 10 per cent bronchial tumours), which represents a sevenfold increase from that recorded by the Swedish National Cancer Register over the same interval (1958–1969). These findings are also consistent with current understanding of the epidemiology of NEN, that there is likely to be a substantial discrepancy between clinically discovered lesions (those reported to a regional or national registry) and their true incidence (asymptomatic, non-diagnosed disease). The autopsy rate was high in the Swedish study²⁶, with 99 per cent of patients who died in hospital and 63 per

cent in general undergoing autopsy. Current autopsy rates in most countries are not comparable and make similar studies difficult^{39,40}.

The observed discrepancy between the present findings together with the Swedish autopsy study²⁶ and the overall reported incidence of GEP-NEN in the literature may have several explanations. Approximately 90 per cent of the neuroendocrine neoplasms identified in the Swedish autopsy study were previously undetected. Clearly, many patients with NEN are asymptomatic and remain undiagnosed, and these tumours may therefore be clinically insignificant^{19,41}. However, the clinical presentation of NETs is often non-specific, and the average delay from onset of symptoms to diagnosis is suggested to be between 5 and 7 years^{42,43}. An increased awareness of NEN among clinicians, radiologists and pathologists, together with widespread use of improved diagnostic tools (such as somatostatin receptor imaging, CT, endoscopies and specific IHC markers), has increased the number of patients with incidentally discovered NEN⁴⁴. These tumours may have gone undetected in the patient's life-time in the Swedish cohort. Demographic changes that include an ageing population might also contribute to this increase, because the frequency of NEN increases with age²², as also shown here. Finally, the increased incidence has also been attributed in part to improved pathological classification; a greater proportion of previously undifferentiated carcinomas are now recognized as NECs³⁷.

A concern related to epidemiological figures from cancer registries (such as the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database and the Cancer Registry of Norway) is that the recording of NEN is usually restricted to 'malignant carcinoids', thereby disregarding benign tumours and NEN with uncertain malignant potential, as noted by Hauso and colleagues⁴⁵. A rather low, although increasing, annual incidence of GEP-NEN of 2.38 per 100 000 (USA 2000; for interval 2000–2004), as can be calculated from that study⁴⁵, is explained mainly by under-reporting to the registry.

Data collection over long intervals introduces bias of disease definitions and classifications²². A lower incidence of GEP-NEN is usually reported from other series. A French study¹⁵ found an annual age-adjusted (world) incidence rate associated with malignant digestive NEN (pancreatic lesions included) of 0.76 per 100 000 men and 0.50 per 100 000 women. The study had a higher median age and a smaller proportion of appendiceal tumours than the present investigation. Although an increasing incidence was observed (1976–1999), differences between these two studies can be explained mainly by the fact

that only malignant tumours were included in the French analysis¹⁶. A prospective 1-year audit of GEP-NEN from Austria¹³ reported an annual age-adjusted incidence rate (USA 2000) of 2.99 per 100 000 inhabitants. Tumours were most frequently located in the stomach, whereas the small bowel was less commonly affected. Although the authors assumed a high degree of completeness of the data, one-quarter of the 41 institutions involved did not report any patients, suggesting possible detection bias. Finally, a study from the Netherlands Cancer Registry³⁷ reported an age-standardized (with respect to European standardized rate) increase in the incidence of NEN from 2.1 in 1990 to 4.9 per 100 000 inhabitants in 2010. Although this supports an increasing incidence, the lower reported incidence is again likely to be explained by a reporting bias towards malignant disease.

The well defined, controlled sample and the centralized infrastructure of the healthcare system in the region serves as an excellent basis for epidemiological research, and is a strength of the present study. The present data obviously contrast with publications from tertiary referral centres, which have an inherent selection bias towards overt malignant and difficult-to-manage cases, which might impede data interpretation. Patient migration out of the region is minimal, which limits the influence of regional referral patterns, different treatment policies or patients diagnosed at other institutions. The most updated definitions and classifications of GEP-NEN have been used. To ensure appropriate comparison of incidence data, commonly used reference populations²² were employed.

Limitations of this study are the size of the population at risk, the retrospective design and the accrual period of 11 years. However, the transparent and controlled access to data in the study region is probably superior to collection of general data reported to a national registry. The period of 11 years should also allow fairly comparable diagnostic opportunities, whereas a longer lag time would potentially increase the variability in diagnostic approach.

Comparing the present high and increasing incidence of GEP-NEN in south-western Norway with recently published data from various regions, it is evident that appropriate identification and reporting of patients with NEN remain a challenge.

Acknowledgements

The authors thank E. Hoel of Statistics Norway, Oslo, for providing detailed demographic data on the Norwegian population during the study period. They are also indebted to the late Professor Michael Brauckhoff for providing pertinent data on some of the included patients, who were managed partially at Haukeland University Hospital,

Bergen. This study was financed partly by an unrestricted research grant provided by CarciNor, the Norwegian patient advocacy association for NEN.

Disclosure: The authors declare no conflict of interest.

References

- 1 Lepage C, Bouvier AM, Faivre J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. *Eur J Endocrinol* 2013; **168**: R77–R83.
- 2 Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE *et al*. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35 825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063–3072.
- 3 Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann NY Acad Sci* 2004; **1014**: 13–27.
- 4 Langhans T. Über einen Drüsenpolyp im Ileum. *Archiv F Pathol Anat* 1867; **38**: 559–560.
- 5 Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet* 1963; **1**: 238–239.
- 6 Soga J, Tazawa K. Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases. *Cancer* 1971; **28**: 990–998.
- 7 Pearse AG. The diffuse neuroendocrine system and the apud concept: related 'endocrine' peptides in brain, intestine, pituitary, placenta, and anuran cutaneous glands. *Med Biol* 1977; **55**: 115–125.
- 8 Rindi G, Kloppel G, Couvelard A, Komminoth P, Körner M, Lopes JM *et al*. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; **451**: 757–762.
- 9 Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW *et al*. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395–401.
- 10 Rindi G, Arnold R, Bosman FT, Capella C, Klimstra DS, Klöppel G *et al*. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In *WHO Classification of Tumours of the Digestive System*, Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). International Agency for Research on Cancer: Lyon, 2010; 13–14.
- 11 Sobin LH, Gospodarowicz MK, Wittekind C (eds). *International Union Against Cancer (UICC). TNM Classification of Malignant Tumours* (7th edn). Wiley-Blackwell: Oxford, 2009.
- 12 Westergaard T, Frisch M, Melbye M. Carcinoid tumors in Denmark 1978–1989 and the risk of subsequent cancers. A population-based study. *Cancer* 1995; **76**: 106–109.
- 13 Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; **17**: 909–918.

- 14 Levi F, Te VC, Randimbison L, Rindi G, La Vecchia C. Epidemiology of carcinoid neoplasms in Vaud, Switzerland, 1974–97. *Br J Cancer* 2000; **83**: 952–955.
- 15 Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* 2004; **53**: 549–553.
- 16 Lepage C, Bouvier AM, Manfredi S, Dancourt V, Faivre J. Incidence and management of primary malignant small bowel cancers: a well-defined French population study. *Am J Gastroenterol* 2006; **101**: 2826–2832.
- 17 Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1–18, vii.
- 18 Landerholm K, Falkmer S, Jarhult J. Epidemiology of small bowel carcinoids in a defined population. *World J Surg* 2010; **34**: 1500–1505.
- 19 Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W *et al.* Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. *J Gastroenterol* 2010; **45**: 234–243.
- 20 Ito T, Igarashi H, Nakamura K, Sasano H, Okusaka T, Takano K *et al.* Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol* 2015; **50**: 58–64.
- 21 Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer* 2001; **92**: 2204–2210.
- 22 Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, Knowledge N. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocr Relat Cancer* 2014; **21**: R153–R163.
- 23 Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 2010; **105**: 2563–2569.
- 24 Crocetti E. Gastrointestinal carcinoid tumours. A population-based study. *Ital J Gastroenterol Hepatol* 1997; **29**: 135–137.
- 25 Caldarella A, Crocetti E, Paci E. Distribution, incidence, and prognosis in neuroendocrine tumors: a population based study from a cancer registry. *Pathol Oncol Res* 2011; **17**: 759–763.
- 26 Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. *Acta Pathol Microbiol Scand A* 1976; **84**: 322–330.
- 27 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; **335**: 806–808.
- 28 Statistics Norway. <http://www.ssb.no> [accessed 20 October 2014].
- 29 Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2011; **18**(Suppl 1): S1–S16.
- 30 Doll R. Comparison between registries. Age-standardized rates. In *Cancer Incidence in Five Continents*, Waterhouse J, Muir C, Correa P, Powell P (eds). International Agency on Cancer: Lyon, 1976; 453–459.
- 31 Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. *Healthy People 2010 Stat Notes* 2001; (20): 1–10.
- 32 Ahmad OB, Boschi-Pinto C, Lopez A, Murray CJ, Lozano R, Inoue M. *Age Standardization of Rates: a New WHO Standard*. World Health Organization: Geneva, 2001.
- 33 Eurostat European Commission. *Revision of the European Standard Population: Report of Eurostat's Task Force*; 2013. <http://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f> [accessed 30 September 2015].
- 34 Aragon TJ (developer). *EpiTools: Epidemiology Tools. R package version 0.5-7*; 2012. <http://CRAN.R-project.org/package=epitools> [accessed 30 September 2015].
- 35 Holt N, Grønbaek H. Goblet cell carcinoids of the appendix. *Scientific World Journal* 2013; **2013**: 543696.
- 36 Roy P, Chetty R. Goblet cell carcinoid tumors of the appendix: an overview. *World J Gastrointest Oncol* 2010; **2**: 251–258.
- 37 Korse CM, Taal BG, van Velthuisen ML, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. *Eur J Cancer* 2013; **49**: 1975–1983.
- 38 van der Zwan JM, Trama A, Otter R, Larrañaga N, Tavilla A, Marcos-Gragera R *et al.* Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. *Eur J Cancer* 2013; **49**: 2565–2578.
- 39 Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet* 2007; **369**: 1471–1480.
- 40 Shojania KG, Burton EC. The vanishing nonforensic autopsy. *N Engl J Med* 2008; **358**: 873–875.
- 41 Niederle MB, Niederle B. Diagnosis and treatment of gastroenteropancreatic neuroendocrine tumors: current data on a prospectively collected, retrospectively analyzed clinical multicenter investigation. *Oncologist* 2011; **16**: 602–613.
- 42 Schimmack S, Svejda B, Lawrence B, Kidd M, Modlin IM. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg* 2011; **396**: 273–298.
- 43 Öberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. *Cancer Metastasis Rev* 2011; **30**(Suppl 1): 3–7.
- 44 Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26**: 803–818.
- 45 Hauso Ø, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK *et al.* Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* 2008; **113**: 2655–2664.